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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte THUAN QUOC TRINH and CHRISTIAN ELLIOTT GRUBER

Appeal 2007-3369
Application 09/306,986
Technology Center 1600

Decided: April 22, 2008

Before, TONI R. SCHEINER, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for anticipation and obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

The following claim 8 is representative.

8. A method for synthesizing a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising:

a) mixing the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity, wherein said peptides or polypeptides having ribonuclease activity are capable of degrading single-stranded RNA; and

b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and under which said peptides or polypeptides having ribonuclease activity degrade said single-stranded RNA.

References Cited by the Examiner:

Joseph G. Major, Jr., "A Rapid PCR Method of Screening for Small Mutations," 12(1) *BioTechniques*, 40, 42-43 (1992). (hereinafter Major)

Atilio Deana & Joel G. Belasco, "The Function of RNase G in Escherichia coli is constrained by its amino and carboxyl termini," 51(4), *Molecular Microbiology*, 1205-1217 (2004). (hereinafter Deana and Belasco)

Tom Maudru & Keith Peden, "Elimination of Background Signals in a Modified Polymerase Chain Reaction-Based Reverse Transcriptase Assay," 66 *Journal of Virological Methods* 247-261 (1997). (hereinafter Maudru)

Grounds of Rejection

1. Claims 8-12, 56, and 70-73 stand rejected under 35 U.S.C. § 102(b), over Major in view of Deana and Belasco.

2. Claims 8-12, 56, 70, 71, and 73 stand rejected under 35 U.S.C. § 103(a), over Major in view of Maudru.

DISCUSSION

Background

"Applicants have found that the problems associated with nucleic acid synthesis (particularly for PCR) from crude preparations may be due to the abundance of RNA in such crude DNA preparations. Consequently, the present invention provides compositions and methods for synthesizing polynucleotides in the presence of ribonucleases." (Spec. 2.)

1. Claims 8-12, 56, and 70-73 stand rejected under 35 U.S.C. § 102(b), over Major in view of Deana and Belasco.

The Examiner alleges that

> Major teaches a rapid PCR method of screening for point mutations. … Major teaches a method which comprises the synthesis of a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising mixing the preparation with one or more DNA polymerases and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of a template nucleic acid molecule. The method taught by Major specifically involves the PCR amplification, using Taq DNA polymerase, of a DNA fragment from the expression plasmid, pBluescript 11 SK(+), either sampled directly from JM109 *E. coli* colonies or from a bacterial plasmid isolate. Major further teaches that some primers, especially those with a 3'-terminal T-'T mismatch result in extra minor bands when bacterial colony lysates were used for the starting material. This thus decreases the sensitivity of the taught assay.

(Ans. 3.)

The Examiner acknowledges that "Major does not teach the inclusion of ribonuclease in the taught method", (*id.* at 3-4) however, argues that the bacterial lysate mixture taught by Major et al. inherently comprises ribonuclease. (*Id.* at 4.)

To support the inherency position, the Examiner relies on Deana and Belasco which teaches that *E. coli* inherently comprises a number of RNases that are capable of degrading single stranded RNA. (Deana and Belasco, abstract.)

Appellants contend that "because a clarified bacterial colony lysate does not necessarily contain RNAases, the Deana and Belasco reference does not support the Examiners inherent anticipation argument." (Br. 8.) Appellants also argue that "even if the Examiner's inherent anticipation argument is correct, there is nothing in the Major reference that teaches [a step of] mixing a preparation comprising RNA and double-stranded DNA with one or more DNA polymerases and one or more peptides or polypeptides having ribonuclease activity, as specified by the currently pending claims." (Br. 8.)

We agree with Appellants and do not find that Major evidences a step of "a) mixing the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity, wherein said peptides or polypeptides having ribonuclease activity are capable of degrading single-stranded RNA," as claimed. In other words, although the original preparation recited in the preamble of the claim may inherently include an RNAase, Major does not disclose a step of mixing that preparation with one or

more polymerases and one or more peptides or polypeptides having ribonuclease activity, as claimed.

In view of the above, we reverse the anticipation rejection in view of Major.

2. Claims 8-12, 56, 70, 71, and 73 stand rejected under 35 U.S.C. § 103(a), over Major in view of Maudru.

Major is discussed herein. According to the Examiner,

> Major does not teach the inclusion of ribonuclease in the taught method of synthesizing nucleic acids. Maudru et al. examine the cause and teach a method for the elimination of background signals in a modified polymerase chain reaction-based reverse transcriptase assay.

(Ans. 5.)

Thus the Examiner relies on Maudru for teaching that

> the background signal of the PCR-based reverse transcriptase (PBRT) assay was due to an intrinsic RNA-dependent DNA polymerase activity of the Taq DNA polymerase enzyme used for the assay. They further teach that this background signal could be eliminated by inserting a ribonuclease digestion step prior to amplifying the cDNA product of the RT reaction by PCR.

(Ans. 5.)

The Examiner concludes that

> [o]ne of ordinary skill in the art at the time of filing would have been motivated to add a polypeptide with ribonuclease activity to the method taught by Major, in order to remove residual RNA sequence contamination from the

> targeted nucleic acid template in any preparation which would contain substantial amounts of RNA, such as a bacterial colony lysate, in order to decrease the level of background signal from the taught PCR assay. As the ordinary artisan would know that any nucleic acid preparation that has not been purified, such as a bacterial colony lysate, contains substantial amounts of contaminating RNA, the motivation for the removal of these contaminating sequences is that this would increase the sensitivity of the taught PCR assay method from bacterial colony lysates, thus eliminating the need for purification of the template DNA and reducing time and work needed to perform the assay. This is supported by both Major, who teach that some primer sets when used with bacterial colony lysates result in extra minor bands, and Maudru et al. who teach that the background signals of PDR [sic, PCR] based nucleic acid synthesis reactions is due to an intrinsic RNA-dependent DNA polymerase activity of Taq DNA polymerase.

(Ans. 6.)

Appellants argue that it is well known in the art that errors in terminal mismatch discrimination occurred in samples that did not contain any RNA. (Br. 15.) Appellants argue that one of ordinary skill in the art "would not have regarded the difference in terminal mismatch discrimination alluded to in Major as being caused by RNA in bacterial colony lysates." (Br. 15.) Appellants further argue that Maudru attributes the presence of background amplification products to an intrinsic RNA-dependent DNA polymerase activity of the DNA polymerase used in the assay. (Br. 11.) Thus Appellants conclude that the background amplification products of Maudru arise for a completely different reason than the "extra minor bands" of Major and thus persons of ordinary skill in the art would not have been motivated to apply Maudru's strategy to reduce background amplification products to address the shortcoming of the Major assay. (Br. 16-17.)

In making an obviousness determination over a combination of prior art references, it is important to identify a reason why persons of ordinary skill in the art would have attempted to make the claimed subject matter. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). When making such a determination, the scope of the prior art and level of ordinary skill must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). We agree with Appellants' reasoning and do not find the Examiner has indicated a sufficient reason, suggestion or motivation to combine the cited references. We do not find that the Examiner has established a sufficient nexus between the "extra minor bands" described in Major's and Maudru's background amplification products to provide a reason to combine the cited references.

The rejection of the claims for obviousness over Major in view of Maudru is reversed.

New Ground of Rejection

Claim 8 is rejected under 35 USC §102(b) over Maudru.

Maudru discloses the method of the claimed invention at page 250 beginning in the bottom of column 1 in the section entitled "2.2.2. *Polymerase chain reaction (PCR)*". This section describes conduction of PCR in the presence of both RNase and thermostable DNA polymerase. Thus Maudru describes a step of "a) mixing the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity, wherein said peptides or polypeptides having ribonuclease activity are capable of degrading single-stranded RNA," as claimed. Because Maudru conducts PCR using a double stranded DNA, Maudru discloses a step of "b) incubating said mixture under conditions

sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and under which said peptides or polypeptides having ribonuclease activity degrade said single-stranded RNA," as claimed. Maudru section 2.2.2. further describes conducting RNAse digestion for 30 min. prior to conducting PCR for 30 min. This procedure is conducted to reduce background signals causes by an intrinsic RNA-dependent DNA polymerase activity of the Taq DNA polymerase, the enzyme used in PCR. (Maudru, abstract.) Thus Maudru anticipates claim 8.

Upon return of the application to the Examiner, the Examiner is encouraged to review the relevance of Maudru to other pending claims alone or in combination with other relevant references.

SUMMARY

The rejections of the claims for anticipation and obviousness are reversed. A new ground of rejection of claim 8 for anticipation over Maudru is made.

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

REVERSED AND 37 C.F.R. § 41.50(b)

Ssc:

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